7 October 2008

This supplement has been prepared to present scientific and technical news items that may be of more interest to technical personnel at RDT&E activities and the labs, or the medics rather than the broader readership of the basic CB Daily. Due to the nature of the material, the articles, if available online, are usually only available through subscription services thus making specific links generally unavailable. Thus, usually only the bibliographic citation is available for use by an activity's technical library.

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Chem-Bio News – Pandemic Influenza Supplement #30

1. FDA CLEARS NEW CDC TEST TO DETECT HUMAN INFLUENZA: *"The Food and Drug Administration (FDA) today cleared a new test developed by the U.S. Centers for Disease Control and Prevention (CDC) to diagnose human influenza infections and the highly pathogenic influenza A (H5N1) viruses."*

2. MEDIMMUNE LICENSES REVERSE GENETICS TECHNOLOGY TO JAPAN'S BIKEN FOR USE IN INFLUENZA VACCINE DEVELOPMENT AND PRODUCTION: *"For potential pandemic influenza vaccines, reverse genetics can be a useful technology because the process does not require manufacturers to work directly with potentially highly infectious pandemic strains, such as H5N1, rather only with segments of the virus's genome."*

3. PLANT CANCELLATION SHOWS PROBLEMS IN FLU VACCINE BUSINESS: *"A flu vaccine manufacturer's decision not to build a US facility has highlighted the perpetual mismatch between flu-shot supply and demand—and the reality that the mismatch may undermine plans for pandemic flu vaccines."*

4. ANNEXIN II INCORPORATED INTO INFLUENZA VIRUS PARTICLES SUPPORTS VIRUS REPLICATION BY CONVERTING PLASMINOGEN INTO PLASMIN: *"Collectively, these results indicate that the annexin II-mediated activation of plasminogen supports the replication of influenza viruses, which may contribute to their pathogenicity."*

5. DEVELOPMENT OF AN HTS ASSAY FOR THE SEARCH OF ANTI-INFLUENZA AGENTS TARGETING THE INTERACTION OF VIRAL RNA WITH THE NS1 PROTEIN: *"These results support the hypothesis that the binding of NS1 to vRNA could be a novel target for the development of anti-influenza drugs."*

6. ROLE OF INITIATING NUCLEOSIDE TRIPHOSPHATE CONCENTRATIONS IN THE REGULATION OF INFLUENZA VIRUS REPLICATION AND TRANSCRIPTION: *"Based on our observations, we propose a new model for the de novo initiation of influenza virus replication."*

7. U.S. PANDEMIC COULD SEVERELY STRAIN FACE MASK, OTHER PPE SUPPLY PIPELINE: *"Fears of an avian influenza or Severe Acute Respiratory Syndrome (SARS)-like*

pandemic in the United States may have subsided somewhat in the years since H5N1 first ravaged parts of Asia, but concerns linger about our nation's supply of face masks should a pandemic erupt."

8. CANBERRA SCIENTIST GRAEME LAVER DEAD AT 79: *"Dr Laver researched the influenza virus for more than 30 years and helped develop the anti-flu drug Relenza."*

CB Daily Report

Chem-Bio News

FDA CLEARS NEW CDC TEST TO DETECT HUMAN INFLUENZA
Infection Control Today Magazine
September 30, 2008

"The Food and Drug Administration (FDA) today cleared a new test developed by the U.S. Centers for Disease Control and Prevention (CDC) to diagnose human influenza infections and the highly pathogenic influenza A (H5N1) viruses.

The device, called the Human Influenza Virus Real-Time RT-PCR Detection and Characterization Panel (rRT-PCR Flu Panel), uses a molecular biology technique to detect flu virus and differentiate between seasonal and novel influenza.

The device is used to isolate and amplify viral genetic material present in secretions taken from a patient's nose or throat. The viral genetic material is labeled with fluorescent molecules, which are then detected and analyzed by a diagnostic instrument called the Applied Biosystems 7500 Fast Dx, also cleared today by the FDA for diagnostic use simultaneously with the CDC's rRT-PCR Flu Panel."

The full article can be found at: http://www.infectioncontroltoday.com/hotnews/new-test-for-human-influenza.html

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MEDIMMUNE LICENSES REVERSE GENETICS TECHNOLOGY TO JAPAN'S BIKEN FOR USE IN INFLUENZA VACCINE DEVELOPMENT AND PRODUCTION
PRNewswire
September 29, 2008

"MedImmune announced today that it has licensed its proprietary reverse genetics intellectual property to BIKEN, The Research Foundation for Microbial Diseases of Osaka University in Japan to support the development and construction of new vaccine strains to produce non-live human influenza vaccines. Reverse genetics is a method by which viruses such as influenza can be generated from segments of DNA. For potential pandemic influenza vaccines, reverse genetics can be a useful technology because the process does not require

manufacturers to work directly with potentially highly infectious pandemic strains, such as H5N1, rather only with segments of the virus's genome."

The full article can be found at: http://www.fiercebiotech.com/press-releases/medimmune-licenses-reverse-genetics-technology-japans-biken-use-influenza-vaccine-d-0

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PLANT CANCELLATION SHOWS PROBLEMS IN FLU VACCINE BUSINESS
By Maryn McKenna
CIDRAP News (Center for Infectious Disease Research & Policy – University of Minnesota)
October 3, 2008

"A flu vaccine manufacturer's decision not to build a US facility has highlighted the perpetual mismatch between flu-shot supply and demand—and the reality that the mismatch may undermine plans for pandemic flu vaccines.

On Tuesday, Solvay Pharmaceuticals Inc. of Marietta, Ga., announced that it was canceling plans to build a US flu-vaccine manufacturing plant, a $386 million project that Birmingham, Ala., and Athens, Ga., have been competing for. The plant would have made both seasonal and pandemic flu vaccines—but at just about the moment when a final site selection was expected, the company announced that the economics of the two-year-old deal no longer make sense."

"In May 2006, the Department of Health and Human Services granted more than $1 billion to five pharmaceutical firms to develop cell-culture technology and manufacturing capacity within the United States. Solvay, one of the five, received $298 million for "the development and testing of new influenza vaccines including pandemic vaccines that are produced using cell-based technology and the development of a master plan to manufacture, formulate, fill and package annual and pandemic influenza vaccines in a new US-based facility," the company said in a press release at the time.

But while the grant covered development and design costs for the new plant, it did not in the end cover enough of the capital costs to make the facility worthwhile, Solvay spokesman Neil Hirsch said in an interview.

The full article can be found at: http://www.cidrap.umn.edu/cidrap/content/influenza/biz-plan/news/oct0308solvay.html

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ANNEXIN II INCORPORATED INTO INFLUENZA VIRUS PARTICLES SUPPORTS VIRUS REPLICATION BY CONVERTING PLASMINOGEN INTO PLASMIN
Biotech Week
October 8, 2008

"For influenza viruses to become infectious, the proteolytic cleavage of hemagglutinin (HA) is essential. This usually is mediated by trypsin-like proteases in the respiratory tract."

"The binding of plasminogen to influenza virus A/WSN/33 leads to the cleavage of HA, a feature determining its pathogenicity and neurotropism in mice. Here, we demonstrate that plasminogen also promotes the replication of other influenza virus strains. The inhibition of the conversion of plasminogen into plasmin blocked influenza virus replication. Evidence is provided that the activation of plasminogen is mediated by the host cellular protein annexin II, which is incorporated into the virus particles. Indeed, the inhibition of plasminogen binding to annexin II by using a competitive inhibitor inhibits plasminogen activation into plasmin."

"Collectively, these results indicate that the annexin II-mediated activation of plasminogen supports the replication of influenza viruses, which may contribute to their pathogenicity."

The full article can be found at: (F. Lebouder, et. al., “Annexin II incorporated into influenza virus particles supports virus replication by converting plasminogen into plasmin”. Journal of Virology, 2008;82(14):6820-6828). Link not available.

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DEVELOPMENT OF AN HTS ASSAY FOR THE SEARCH OF ANTI-INFLUENZA AGENTS TARGETING THE INTERACTION OF VIRAL RNA WITH THE NS1 PROTEIN
Genetics & Environmental Law Weekly
October 11, 2008

"The NS1 protein is a nonstructural protein encoded by the influenza A virus. It is responsible for many alterations produced in the cellular metabolism upon infection by the virus and for modulation of virus virulence."

"The NS1 protein is able to perform a large variety of functions due to its ability to bind various types of RNA molecules, from both viral and nonviral origin, and to interact with several cell factors. With the aim of exploring whether the binding of NS1 protein to viral RNA (vRNA) could constitute a novel target for the search of anti-influenza drugs, a filter-binding assay measuring the specific interaction between the recombinant His-NS1 protein from influenza A virus and a radiolabeled model vRNA (32P-vNSZ) was adapted to a format suitable for screening and easy automation. Flashplate technology (PerkinElmer, Waltham, MA), either in 96-or 384-well plates, was used. The Flashplate wells were precoated with the recombinant His-NS1 protein, and the binding of His-NS1 to a 35S-vNSZ probe was measured. A pilot screening of a collection of 27,520 mixtures of synthetic chemical compounds was run for inhibitors of NS1 binding to vRNA. We found 3 compounds in which the inhibition of NS1 binding to vRNA, observed at submicromolar concentrations, was correlated with a reduction of the cytopathic effect during the infection of cell cultures with influenza virus."

"These results support the hypothesis that the binding of NS1 to vRNA could be a novel

target for the development of anti-influenza drugs."

The full article can be found at: (M. Maroto, et. al., “Development of an HTS assay for the search of anti-influenza agents targeting the interaction of viral RNA with the NS1 protein”. Journal of Biomolecular Screening, 2008;13(7):581-90). Link not available.

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ROLE OF INITIATING NUCLEOSIDE TRIPHOSPHATE CONCENTRATIONS IN THE REGULATION OF INFLUENZA VIRUS REPLICATION AND TRANSCRIPTION
Biotech Week
October 8, 2008

“Previous studies in our laboratory have shown that virion-derived viral ribonucleoprotein complexes synthesize both mRNA and cRNA in vitro and early in the infection cycle in vivo," scientists in Oxford, the United Kingdom report.”

"Our continued studies showed that de novo synthesis of cRNA in vitro is more sensitive to the concentrations of ATP, CTP, and GTP than capped-primer-dependent synthesis of mRNA. Using rescued recombinant influenza A/WSN/33 viruses, we now demonstrate that the 3'-terminal sequence of the vRNA promoter dictates the requirement for a high nucleoside triphosphate (NTP) concentration during de novo-initiated replication to cRNA, whereas this is not the case for the extension of capped primers during transcription to mRNA. In contrast to some other viral polymerases, for which only the initiating NTP is required at high concentrations, influenza virus polymerase requires high concentrations of the first three NTPs. In addition, we show that base pair mutations in the vRNA promoter can lead to nontemplated dead-end mutations during replication to cRNA in vivo."

"Based on our observations, we propose a new model for the de novo initiation of influenza virus replication."

The full article can be found at: (F.T. Vreede, et. al., “ Role of initiating nucleoside triphosphate concentrations in the regulation of influenza virus replication and transcription”. Journal of Virology, 2008;82(14):6902-6910). Link not available.

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U.S. PANDEMIC COULD SEVERELY STRAIN FACE MASK, OTHER PPE SUPPLY PIPELINE
By Kelly M. Pyrek
Infection Control Today Magazine
October 4, 2008

“Fears of an avian influenza or Severe Acute Respiratory Syndrome (SARS)-like pandemic in the United States may have subsided somewhat in the years since H5N1 first ravaged parts

of Asia, but concerns linger about our nation's supply of face masks should a pandemic erupt."

"According to the Pandemic Influenza Plan of the Department of Health and Human Services (DHHS), the U.S. must have a national stockpile of 40 million doses (two doses per person) of vaccine against influenza virus subtypes considered to pose a substantial pandemic risk (currently avian H5N1). Additionally, the plan calls for domestic influenza vaccine manufacturing capacity to produce sufficient pandemic vaccine for the U.S. population within six months of the onset of an influenza pandemic. The plan also calls for the availability of at least 81 million treatment courses of approved antiviral drugs, enough for treatment of approximately one-quarter of the U.S. population, and 6 million additional treatment courses in reserve for domestic containment. The plan alludes briefly to the necessity of maintaining equipment and supplies in the Strategic National Stockpile (SNS) and state stockpiles sufficient to enhance medical surge capacity.

Influenza vaccines and antiviral drugs are normally the first defense against the flu, but availability and immediacy could be problematic during a pandemic. A pandemic may be particularly devastating because human populations will have little, if any, baseline immunity to an entirely new, mutated viral strain. What is critical to remember is that during a pandemic, the primary prevention strategies of vaccines and antiviral prophylaxes are likely to be either unavailable or initially limited in quantity and availability, so reliance upon secondary prevention strategies, including the use of face masks and respiratory etiquette, may be more of a last resort. In the absence of primary prevention, measures to prevent or slow transmission of the virus in both the healthcare and community sectors must be used. Such measures include isolating patients, limiting contacts with infected persons, and otherwise minimizing the likelihood of exposure to the virus, as well as frequent handwashing and requiring infected individuals to be quarantined or equipped with medical masks that might limit respiratory transmission of the virus."

"Chettle paints a picture for us: "In a severe pandemic, millions of desperately ill people needing hospitalization will quickly overwhelm the healthcare system to the point of collapse. There will be an immediate shortage of hospital beds; critical supplies (surgical gloves, masks, gowns, IV bags, and antibiotics); and trained staff to care for patients. For example, in the U.S., there are about 965,300 staffed hospital beds — not nearly enough. During the peak week of a pandemic, the following numbers of staffed beds and ventilators would be needed in the U.S. for influenza patients alone: 191 percent of current non-ICU beds, 461 percent of ICU beds, 198 percent of all available ventilators. Projections of hospitalizations are only estimates. However, the gap between our current resources and our needs is staggering. These numbers assume that 25 percent to 30 percent of the U.S. population will fall sick and that illnesses will be spaced over eight weeks. It is expected that even in the peak weeks of a pandemic, no more than 10 percent of a community's population will be ill at any one time."

The full article can be found at: http://www.infectioncontroltoday.com/articles/pandemic-and-face-mask-shortage.html

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CANBERRA SCIENTIST GRAEME LAVER DEAD AT 79
ABC News
October 6, 2008

"Well-known Canberra scientist Graeme Laver has died in London at the age of 79.

Dr Laver researched the influenza virus for more than 30 years and helped develop the anti-flu drug Relenza.

In 1996, Dr Laver was awarded the Australia Prize for excellence in the field of pharmaceutical design."

The full article can be found at: http://www.abc.net.au/news/stories/2008/10/06/2383122.htm?site=science&topic=latest

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